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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,657	04/18/2005	Karina Drumm	129402.00201	9864

7590 07/12/2006

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *2,12,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13-16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/05; 12/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A, B, and C*.

DETAILED ACTION

Election/Restrictions

Applicants' timely election with traverse of Group III, Claims 1, 3–11, 13–16, and 19-23, in the reply filed on 6/8/06, is acknowledged. Also acknowledged is Applicants' election of SEQ ID NO:3.

The traversal is on the ground(s) that it would not be unduly burdensome to search all claims 1-23 together in the same application. Applicants' arguments have been fully considered but are not found persuasive.

As Applicants note in their response, MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

However, in the instant case, burden is not a factor for consideration.

The instant application is a National Stage Application filed under 35 USC 371(c). Such applications are evaluated according to Unity of invention practice under 37 CFR §1.499 and 1.475. Pursuant to these rules, burden is not a factor that must be considered in the determination of unity of invention.

As explained in the Requirement, Unity of Invention is lacking because the different groups do not share the same or corresponding technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Status of the application

Claims 1–23 are pending. Claims 2, 12, 17, and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 3-11, 13-16, and 19-23 are examined herein.

Claim Objections

Claims 11 and 19 are objected to for being drawn to non-elected inventions. Specifically, claim 11 recites non-elected inhibitors such as polypeptide, antibody, and ligand binding molecule. Claim 19 recites non-elected SEQ ID Nos 1, 2, and 4.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "the pharmaceutical composition." There is insufficient antecedent basis for this limitation in the claim.

Claim 14 is indefinite because it cannot be determined which method in particular the claim is drawn to. The claim recites "The method of claim" but does not provide a claim number.

Thus, it cannot be determined which claim this claim depends from. Consequently, Claims 15 and 16 are indefinite because they depend from claim 14.

Accordingly, claims 14-16 have not been further treated on the merits because it cannot be determined what invention they are drawn to.

***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, 13, and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a method for the treatment of a disorder of the central nervous system and/or eye comprising adminstering to a subject a composition comprising a compound capable of modulating a target gene or gene product in a therapeutically effective amount. Claims 3-4 are drawn to methods thereof wherein the disorder is related to the eye, angiogenesis, neovascularization, retinal pigment epithelium, neurosensory retina, choriodea, macular degeneration, or diabetic retinopathy. Claims 7, 8, and 21-23 specify the route of administration, while claims 9–11 and 20 specify that the compound is a nucleic acid inhibitor or antagonist of

the target gene or gene product. Claim 13 limits the invention to an inhibitor that consists substantially of RNA.

Thus, the claims are extremely broad, encompassing methods of treatment of any CNS or eye disorder, including but not limited to those specifically recited, using any compound capable of modulating (i.e., stimulating or inhibiting) the expression and/or activity of a target gene or gene product, which may virtually any gene or protein or RNA directly or indirectly related to the disorder. Thus, the claims encompass a large genus of methods requiring a multitude of therapeutic compounds of virtually any class, inorganic and organic compounds, small molecule drugs, lipids, carbohydrates, peptides and polypeptides, antibodies, modified and unmodified, single and double stranded RNA and DNA nucleic acids of any length, composition, or conformation, viral vectors and plasmids.

Adequate written description support under 35 USC §112, first paragraph, for the entire genus of methods now claimed does not exist in the instant application. That is, adequate written description support does not exist for the genus of compounds and compositions required to practice the full scope of the invention now claimed. The specification discloses neither a representative number of species compounds nor any structure/function correlation that would enable one of skill to immediately envision the genus of compounds now required to practice the full scope of the invention, as now claimed.

A review of the specification fails to find any description, by words, structures, figures, diagrams, or formulas, of any composition or compound that may be used in the instant methods to treat any CNS or eye-related disorder. While the specification teaches at pages 52-54 that dsRNA targeting GFP may be delivered to the retina of a transgenic mouse via intravenous

injection and that GFP expression in the retina may be reduced by systemic delivery in a mouse, this example is not directed to the treatment of any eye or CNS disorder and does not describe any compound, composition, antisense or siRNA or any vector thereof, nor any other molecule for use in the instant methods to treat an eye or CNS disorder. And while pages 55-58 list several genes, there is no disclosure explaining the relavance of these genes to any particular disorder nor any description of the compounds that are to be used to inhibit or agonize these genes so as to provide a definitive treatment effect. While these genes may indeed be suitable targets for a given disorder, even if one knew which gene was related to any given disorder and whether or not to inhibit or agonize the gene or gene product, one of skill in the art would, nevertheless, be left to de novo screening methods to identify a compound having the desired activity to produce the desired therapeutic effect.

More specifically, with regard the genus of nucleic acid inhibitors, one of skill in the art would not be able to envision the structure of any nucleic acid or any modified variant thereof that would enable one of skill to practice the instant invention because the instant application does not describe any such nucleic acids.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of those specific, structurally and functionally defined dsRNAs disclosed in the specification at pages 52-52, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of organic and inorganic compounds that may be used to treat each of the disorders delineated in the claims, regardless of the complexity or simplicity of the method used to screen for and identify such compounds. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

In the instant case, the specie(s) specifically disclosed is/are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Accordingly, the instant claims are rejected for lack of written description support.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-11, 13, 21–23 are rejected under 35 U.S.C. 102(b) as being anticipated by Robinson et al. (US Patent 5,814,620).

Robinson et al. teach a method for treating diabetic retinopathy and macular degeneration comprising the step of intravitreally administrating to a subject afflicted with diabetic retinopathy

a therapeutic amount of an antisense oligonucleotide specific for vascular endothelial growth factor nucleic acid and effective in inhibiting the expression of vascular endothelial growth factor in the retina, including choroidal neovascularization (claim 1 and Examples 4 and 5, column 15, for example). Several representative embodiments of anti-VEGF oligonucleotides are disclosed at Table 1, column 6). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5). They may be combined with a variety of pharmaceutically acceptable carriers and formulated in pyrogen-free compositions in a way suitable for intraocular or intravitreal or systemic administration (column 10, lines 20-40; column 11, lines 5-15). For example, the antisense oligonucleotide may be formulated as a sterile, buffered, isotonic solution (column 10, lines 20-35).

Accordingly, the instant claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al, Dryja et al. (US Patent 5,498,521), Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268, and Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33.

Claim 19 is drawn to the method of claim 1, wherein the gene target comprises a cDNA comprising a nucleotide sequence of SEQ ID NO:3. Claim 20 is drawn to the method of claim 1 wherein the compound is a nucleic acid molecule designed to be expressed in cells of the eye or CNS.

Robinson et al. are relied on for the reasons given above and for those stated herein. Robinson et al. teach methods for delivering antisense oligonucleotides intraocularly to cells in the eye to treat diseases associated with the eye. Robinson et al. teach specifically methods for targeting VEGF in retinal cells using intravitreal administration of antisense oligonucleotides

targeting VEGF. Robinson et al. do not teach antisense oligonucleotides or vectors expressing oligonucleotides targeting SEQ ID NO:3.

The instant application teaches that SEQ ID NO:3 corresponds to the beta-subunit of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (page 18), which is 3283 nucleotides in length. A standard search of SEQ ID NO:3 finds that SEQ ID NO:3 corresponds to GenBank Accession No. S41458, which is 3231 nucleotides in length (see search result in Exhibit A). A comparison of NM_000283 and S41458 shows that NM_000283 comprises S41458 (compare Exhibit B and C).

Weber et al. teach the full length sequence of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (See Exhibit C)

Dryja et al. teach methods diagnosing in a mammal, e.g., a human subject, an increased likelihood of, inclination toward, or susceptibility to developing a disease, e.g., retinitis pigmentosa, in which a mutant form of a human photoreceptor protein is a causative agent. Human photoreceptor proteins said to be potential causative agents include the beta subunit of rod retinal cGMP phosphodiesterase (column 2, top). Dryja et al. teach that mutant photoreceptor proteins such as cGMP phosphodiesterase may be involved in hereditary retinal degenerative diseases in which progressive, bilateral degeneration of retinal structures leads to loss of retinal function; these diseases include, for example, age-related macular degeneration (column 1). In an exemplary embodiment, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase corresponding to the gene disclosed by Weber et al. (see Example 9, column 15, lines 35-45), which, as explained above, also corresponds to SEQ ID NO:3. It was found that patients with

mutations in the PDE .beta. gene had clinical findings typical of retinitis pigmentosa (column 17, top). Accordingly, Dryja et al. suggest that the expression of a mutant form of the protein encoded by SEQ ID NO:3 is associated with a disorder of the eye.

Epstein et al. teach the use of antisense inhibitors for specifically regulating phosphodiesterase genes, both *in vitro* and *in vivo*. It is taught for example that the goal of antisense technology is to develop small oligonucleotides, plasmids, or retroviral vectors that can be introduced into cells in order to inhibit gene products specifically. Epstein et al. teach that antisense oligos can be used to inhibit essentially any isoform of PDE (page 21). Epstein et al. provide a complete blueprint for the design and preparation of antisense oligonucleotides against the known PDE gene sequences (see pages 22-25). Epstein et al. state that a number of excellent reviews have been written recently that describe the characteristics of the different PDE isoforms, their regulation, function, and progress in development of pharmacological inhibitors of PDE as therapeutic agents (page 21, 2nd column). Epstein et al. cite a number of additional references as support therein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use antisense oligonucleotides targeting SEQ ID NO:3, corresponding to beta subunit of rod cGMP phosphodiesterase to inhibit the expression of mutant isoforms of SEQ ID NO:3 and consequent development of ocular diseases associated with the expression of mutant isoforms of SEQ ID NO:3.

One would have been both well motivated and have had a reasonable expectation of success given that Dryja et al. teach that mutant isoforms of beta phosphodiesterase (i.e., SEQ ID NO:3) may predispose individuals to macular degeneration, and given that both Robinson et al.

teach that antisense compounds may be used effectively in retinal cells specifically to inhibit the expression of genes associated with macular degeneration, and given that Epstein teaches that antisense compounds may be used effectively to inhibit the expression of phosphodiesterases in particular. One would have had a reasonable expectation of success in targeting mutant forms of SEQ ID NO:3 as well as SEQ ID NO:3 itself given that Dryja et al. teach both the wild type form, as disclosed in Weber et al., and common mutations thereof leading to eye-related disease (see example 9).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Peter Paras, can be reached at telephone number 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

June 28, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635

Exhibit A
STANDARD SEARCH SEQ ID No: 3

OM nucleic - nucleic search, using sw model

Run on: June 24, 2006, 20:18:31 ; Search time 17487 Seconds
(without alignments)
11815.298 Million cell updates/sec

Title: US-10-511-657-3
Perfect score: 3231
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Scoring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

Searched: 6366136 seqs, 31973710525 residues

Total number of hits satisfying chosen parameters: 12732272

RESULT 3
S41458
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DEFINITION rod cGMP phosphodiesterase beta-subunit [human, mRNA, 3231 nt].
ACCESSION S41458
VERSION S41458.1 GI:252252
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
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Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 3231)
AUTHORS Collins,C., Hutchinson,G., Kowbel,D., Riess,O., Weber,B. and
Hayden,M.R.
TITLE The human beta-subunit of rod photoreceptor cGMP phosphodiesterase:
complete retinal cDNA sequence and evidence for expression in brain
JOURNAL Genomics 13 (3), 698-704 (1992)
PUBMED 1322354
REMARK GenBank staff at the National Library of Medicine created this
entry [NCBI gibbsq 109783] from the original journal article.
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ORIGIN

  Query Match             100.0%;  Score 3231;  DB 5;  Length 3231;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 3231;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1
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Qy         241
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Qy         301
CTCTTCATGTACCGCCAGCGCAACGGCGTGGCCGAGCTGGCCACCAGGCTTTTCAGCGTG 360

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Qy         361
CAGCCGGACAGCGTCCTGGAGGACTGCCTGGTGCCCCCCGACTCCGAGATCGTCTTCCCA 420

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Qy         421
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Qy         481
GTGGCCGAGTGCCCTCACTTCAGCTCATTTGCTGACGAGCTCACTGACTACAAGACAAAG 540

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Db         481
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Qy         541
AATATGCTGGCCACACCCATCATGAATGGCAAAGACGTCGTGGCGGTGATCATGGCAGTG 600
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Qy        601
AACAAGCTCAACGGCCCATTCTTCACCAGCGAAGACGAAGATGTGTTCTTGAAGTACCTG 660

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Qy        661
AATTTTGCCACGTTGTACCTGAAGATCTATCACCTGAGCTACCTCCACAACTGCGAGACG 720

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Qy        721
CGCCGCGGCCAGGTGCTGCTGTGGTCGGCCAACAAGGTGTTTGAGGAGCTGACGGACATC 780

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Qy        781
GAGAGGCAGTTCCACAAGGCCTTCTACACGGTGCGGGCCTACCTCAACTGCGAGCGGTAC 840

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Qy        841
TCCGTGGGCCTCCTGGACATGACCAAGGAGAAGGAATTTTTTGACGTGTGGTCTGTGCTG 900

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Db        841
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Qy        901
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Qy        961
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Db        961
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Qy       1021
TCAGCCGATCACTGGGCCCTGGCCAGCGGCCTTCCAAGCTACGTGGCAGAAAGCGGCTTT 1080
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Qy        1081
ATTTGTAACATCATGAATGCTTCCGCTGACGAAATGTTCAAATTTCAGGAAGGGGCCCTG 1140

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Db        1081
ATTTGTAACATCATGAATGCTTCCGCTGACGAAATGTTCAAATTTCAGGAAGGGGCCCTG 1140

Qy        1141
GACGACTCCGGGTGGCTCATCAAGAATGTGCTGTCCATGCCCATCGTCAACAAGAAGGAG 1200

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Db        1141
GACGACTCCGGGTGGCTCATCAAGAATGTGCTGTCCATGCCCATCGTCAACAAGAAGGAG 1200

Qy        1201
GAGATTGTGGGAGTCGCCACATTTTACAACAGGAAAGACGGGAAGCCCTTTGACGAACAG 1260

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Db        1201
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Qy        1261
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Qy        1321
ACCTACGACAAGATGAACAAGCTGGAGAACCGCAAGGACATCGCACAGGACATGGTCCTT 1380

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Qy        1381
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Qy        1501
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Qy        1561
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Qy        1621
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Qy        1681
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Qy        1741
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Db        1741
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Qy        1801
GGCCTGTGCCATGACATCGACCACCGCGGCACCAACAACCTGTACCAGATGAAGTCCCAG 1860

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Qy        1861
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Qy        1921
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Qy        1981
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Qy        2041
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Qy        2101
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Qy        2281
CAGCCCATTCCTATGATGGACCGGAACAAGGCGGCCGAGCTCCCCAAGCTGCAAGTGGGC 2340

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Qy        2341
TTCATCGACTTCGTGTGCACATTCGTGTACAAGGAGTTCTCTCGTTTCCACGAAGAGATC 2400

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Qy        2401
CTGCCCATGTTCGACCGACTGCAGAACAATAGGAAAGAGTGGAAGGCGCTGGCTGATGAG 2460

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Qy        2461
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Qy        2521
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Qy        2581
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Qy        2641
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Qy        2701
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Qy        2761
CACCCAGGCTGGAGTGCCGTGGCACGATCTCAGCTCACTGCAACCTCCACCTCCCAGGTT 2820

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Qy        2881
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Qy        2941
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Qy       3001
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Qy       3061
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Qy       3121
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Db       3121
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Qy       3181 AGATGGACACAGGCCGTTTCTCATCCAGTTTAGGAAAACACACATGCTCAG 3231
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Db       3181 AGATGGACACAGGCCGTTTCTCATCCAGTTTAGGAAAACACACATGCTCAG 3231
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Exhibit B

1: S41458. Reports rod cGMP phosphod...[gi:252252] Links

Features Sequence

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LOCUS       S41458                  3231 bp    mRNA    linear   PRI 08-MAY-1993
DEFINITION  rod cGMP phosphodiesterase beta-subunit [human, mRNA, 3231 nt].
ACCESSION   S41458
VERSION     S41458.1  GI:252252
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3231)
  AUTHORS   Collins,C., Hutchinson,G., Kowbel,D., Riess,O., Weber,B. and
            Hayden,M.R.
  TITLE     The human beta-subunit of rod photoreceptor cGMP phosphodiesterase:
            complete retinal cDNA sequence and evidence for expression in brain
  JOURNAL   Genomics 13 (3), 698-704 (1992)
   PUBMED   1322354
  REMARK    GenBank staff at the National Library of Medicine created this
            entry [NCBI gibbsq 109783] from the original journal article.
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ORIGIN

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Apr 11 2006 19:57:30

Exhibit C

1: NM_000283. Reports Homo sapiens phos...[gi:105990536] Links

Comment Features Sequence

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            (PDE6B), mRNA.
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REFERENCE   1  (bases 1 to 3283)
  AUTHORS   Lerner,L.E., Gribanova,Y.E., Whitaker,L., Knox,B.E. and Farber,D.B.
  TITLE     The rod cGMP-phosphodiesterase beta-subunit promoter is a specific
            target for Sp4 and is not activated by other Sp proteins or CRX
  JOURNAL   J. Biol. Chem. 277 (29), 25877-25883 (2002)
   PUBMED   11943774
  REMARK    GeneRIF: Sp4 is a strong activator of transcription from the
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REFERENCE   2  (bases 1 to 3283)
  AUTHORS   Mou,H., Grazio,H.J. III, Cook,T.A., Beavo,J.A. and Cote,R.H.
  TITLE     cGMP binding to noncatalytic sites on mammalian rod photoreceptor
            phosphodiesterase is regulated by binding of its gamma and delta
            subunits
  JOURNAL   J. Biol. Chem. 274 (26), 18813-18820 (1999)
   PUBMED   10373499
REFERENCE   3  (bases 1 to 3283)
  AUTHORS   Bennett,J., Tanabe,T., Sun,D., Zeng,Y., Kjeldbye,H., Gouras,P. and
            Maguire,A.M.
  TITLE     Photoreceptor cell rescue in retinal degeneration (rd) mice by in
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  JOURNAL   Nat. Med. 2 (6), 649-654 (1996)
   PUBMED   8640555
REFERENCE   4  (bases 1 to 3283)
  AUTHORS   Suslova,V.A., Suslov,O.N., Kim,E.E. and Lipkin,V.M.
  TITLE     [Organization of the gene for the beta-subunit of human
            photoreceptor cyclic GMP phosphodiesterase]
  JOURNAL   Bioorg. Khim. 22 (4), 256-263 (1996)
   PUBMED   8768262
REFERENCE   5  (bases 1 to 3283)
  AUTHORS   McLaughlin,M.E., Ehrhart,T.L., Berson,E.L. and Dryja,T.P.
  TITLE     Mutation spectrum of the gene encoding the beta subunit of rod
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phosphodiesterase among patients with autosomal recessive retinitis pigmentosa
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 92 (8), 3249-3253 (1995)
PUBMED 7724547
REFERENCE 6 (bases 1 to 3283)
AUTHORS Khramtsov,N.V., Feshchenko,E.A., Suslova,V.A., Shmukler,B.E., Terpugov,B.E., Rakitina,T.V., Atabekova,N.V. and Lipkin,V.M.
TITLE The human rod photoreceptor cGMP phosphodiesterase beta-subunit. Structural studies of its cDNA and gene
JOURNAL FEBS Lett. 327 (3), 275-278 (1993)
PUBMED 8394243
REFERENCE 7 (bases 1 to 3283)
AUTHORS McLaughlin,M.E., Sandberg,M.A., Berson,E.L. and Dryja,T.P.
TITLE Recessive mutations in the gene encoding the beta-subunit of rod phosphodiesterase in patients with retinitis pigmentosa
JOURNAL Nat. Genet. 4 (2), 130-134 (1993)
PUBMED 8394174
REFERENCE 8 (bases 1 to 3283)
AUTHORS Khramtsov,N.V., Feshchenko,E.A., Suslova,V.A., Terpugov,B.E., Rakitina,T.V., Atabekova,N.V., Shmukler,B.E. and Lipkin,V.M.
TITLE [Structural studies of cDNA and the gene for the beta-subunit of cGMP phosphodiesterase from human retina]
JOURNAL Bioorg. Khim. 18 (12), 1551-1554 (1992)
PUBMED 1338685
REFERENCE 9 (bases 1 to 3283)
AUTHORS Catty,P., Pfister,C., Bruckert,F. and Deterre,P.
TITLE The cGMP phosphodiesterase-transducin complex of retinal rods. Membrane binding and subunits interactions
JOURNAL J. Biol. Chem. 267 (27), 19489-19493 (1992)
PUBMED 1326553
REFERENCE 10 (bases 1 to 3283)
AUTHORS Collins,C., Hutchinson,G., Kowbel,D., Riess,O., Weber,B. and Hayden,M.R.
TITLE The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain
JOURNAL Genomics 13 (3), 698-704 (1992)
PUBMED 1322354
REFERENCE 11 (bases 1 to 3283)
AUTHORS Altherr,M.R., Wasmuth,J.J., Seldin,M.F., Nadeau,J.H., Baehr,W. and Pittler,S.J.
TITLE Chromosome mapping of the rod photoreceptor cGMP phosphodiesterase beta-subunit gene in mouse and human: tight linkage to the Huntington disease region (4p16.3)
JOURNAL Genomics 12 (4), 750-754 (1992)
PUBMED 1315306
REFERENCE 12 (bases 1 to 3283)
AUTHORS Bateman,J.B., Klisak,I., Kojis,T., Mohandas,T., Sparkes,R.S., Li,T.S., Applebury,M.L., Bowes,C. and Farber,D.B.
TITLE Assignment of the beta-subunit of rod photoreceptor cGMP phosphodiesterase gene PDEB (homolog of the mouse rd gene) to human chromosome 4p16
JOURNAL Genomics 12 (3), 601-603 (1992)
PUBMED 1313787
REFERENCE 13 (bases 1 to 3283)
AUTHORS Weber,B., Riess,O., Hutchinson,G., Collins,C., Lin,B.Y., Kowbel,D., Andrew,S., Schappert,K. and Hayden,M.R.
TITLE Genomic organization and complete sequence of the human gene encoding the beta-subunit of the cGMP phosphodiesterase and its localisation to 4p 16.3
JOURNAL Nucleic Acids Res. 19 (22), 6263-6268 (1991)

PUBMED 1720239
REFERENCE 14 (bases 1 to 3283)
AUTHORS Farber,D.B. and Lolley,R.N.
TITLE Enzymic basis for cyclic GMP accumulation in degenerative photoreceptor cells of mouse retina
JOURNAL J Cyclic Nucleotide Res 2 (3), 139-148 (1976)
PUBMED 6493
REFERENCE 15 (bases 1 to 3283)
AUTHORS Farber,D.B. and Lolley,R.N.
TITLE Cyclic guanosine monophosphate: elevation in degenerating photoreceptor cells of the C3H mouse retina
JOURNAL Science 186 (4162), 449-451 (1974)
PUBMED 4369896
COMMENT VALIDATED REFSEQ: This record has undergone preliminary review of the sequence, but has not yet been subject to final review. The reference sequence was derived from BC000249.1, AC107464.5 and S41458.1.
On Jun 1, 2006 this sequence version replaced gi:4505668.

Summary: Mice homozygous for the rd mutation display hereditary retinal degeneration which has been considered a model for human retinitis pigmentosa. In affected animals, the retinal rod photoreceptor cells begin degenerating at about postnatal day 8, and by 4 weeks no photoreceptors are left. Farber and Lolley (1974, 1976) showed that degeneration is preceded by accumulation of cyclic GMP in the retina and is correlated with deficient activity of the rod photoreceptor cGMP-phosphodiesterase. Bennett et al. (1996) tested the possibility of altering the course of retinal degeneration through subretinal injection of recombinant replication defective adenovirus that contained the murine cDNA for wildtype beta-PDE. Subretinal injection of rd mice was carried out 4 days after birth, before the onset of rd retinal degeneration. Following therapy, beta-PDE transcripts and enzyme activity were detected, and histologic studies revealed that photoreceptor cell death was significantly retarded. [supplied by OMIM].
COMPLETENESS: complete on the 3' end.

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